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COMPUTER-AIDED PREDICTION OF MULTI-TARGET PROFILES: CASE STUDIES FOR CLOZAPINE AND DASATINIB

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Multi-target drugs are the 'sweet spot' of drug discovery [1], due to overlapping between many pathways, which are interesting from the pharmacological point of view. Identifying multi-target profile of the drug is important, to exploit the full therapeutic potential and minimize toxicity [2]. Experimental study of multi-target drug profile is rather expensive and may provide the coverage of the relatively small part of ample pharmacological space. Thus, computational methods may help to identify the most promising fields of experimental research.

The aim of our work is comparing different computational methods predicted biological activity profiles from structural formula of the drug-like compound.

We selected Clozapine and Dasatinib for this case study because these two molecules are known to have exceptionally broad biological activity profiles (according to the Biological Test Results from PubChem, Clozapine and Dasatinib bind with 64 and 149 proteins, respectively).

The majority of computational tools freely available via the Internet, which predict biological activity profiles from structural formula of a molecule, use the ligand-based drug design approach. They include: ChemProt (http://potentia.cbs.dtu.dk/ChemProt/), SuperPred (http://prediction.charite.de/), SEA (http://sea.bkslab.org/), SwissTargetPrediction (http://swisstargetprediction.ch/), TargetHunter (http://cbligand.org/TargetHunter/), PASS Online (http://www.way2drug.com/PASSOnline/). Biological activity profiles predicted by these tools were compared to the experimental information.

According to the predictive accuracy, the studied web-services could be arranged in the following order: SuperPred (22/0) < SwissTargetPrediction (15/15) < TargetHunter (14/51) < PASS (51/47) < ChemProt (148/46) < SEA (131/64). The records in the parentheses separated by slash represent the numbers of correctly predicted targets for Dasatinib and Clozapine, respectively.

Besides, we considered the commercially available software LigandScout, carried out the prediction based on pharmacophore models. Using the information extracted from PubChem, DrugBank, and Integrity, we developed several dozens of pharmacophore models reflecting ligand-targets binding of Clozapine and Dasatinib. Then, we predicted the appropriate biological activities for those two drugs and compared the estimated and known data. It was shown that pharmacophore models created with LigandScout also provide good performance for the studied targets.

We will discuss the influence of computational method and comprehensiveness of the training set on the accuracy of prediction obtained in our case study.

1. Brown D. et al., *Drug Discov. Tod*ay, 2003, **8**: 1067-1077.
2. Rix U. et al., *Nat. Chem. Biol.*, 2009, **5**: 616-624.

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